

**Re"evolutionary" regenerative medicine.**

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**Public Summary:**

The potential to regenerate our damaged limbs and hearts seems the subject of science fiction, but newts and zebrafish do it all the time. Can we learn from these simple creatures? Why have mammals not retained this remarkably useful property in the course of evolution? Can an evolutionary perspective on the mechanisms employed by 'lowly' organisms inform our approach to human tissue regeneration? Could this lead to the generation of abundant patient-specific differentiated cells for cell therapy, for elucidating disease mechanisms, for therapeutic drug screening? Recent studies suggest that this is possible. We propose a re'evolutionary approach to regenerative medicine that involves the transient dual knockdown of tumor suppressors, ARF and Rb, enabling the creation of newly proliferative cells by dedifferentiating our fully specialized, non-dividing cells. This dedifferentiation would address one critical obstacle to translating the potent regenerative capabilities of newts to mammals. The adaptation of a mechanism that nature has previously designed and successfully exploited is highly appealing. We postulate that dedifferentiation ala newt may provide insights into human disease, lead to drug discovery, and a means for regenerating tissues.

**Scientific Abstract:**

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